Remarks

Reconsideration of this Application is respectfully requested.

Claims 1-84 are pending in the application, with claims 1, 66, 69, and 81 being the independent claims. Claims 1 and 35 are sought to be amended. Support for the amendment to claim 1 is found, *inter alia*, at page 8, paragraphs [0018]-[0019] of the specification as originally filed. Applicants point to paragraph [0018] of the Specification for what is meant by "traditional homologous recombination." Support for the amendment to claim 35 is found throughout the specification and claims as originally filed. Because the Examiner has made the restriction requirement final, claims 46-47, 66-68, and 81-84 have been canceled without prejudice. Applicants reserve the right to pursue the canceled subject matter in related applications. Claims 21, 23, 28, 36, 37, 39, 42, 43, 45-58, and 63-84 have been withdrawn from consideration by the Examiner as being drawn to non-elected inventions or non-elected species, but remain pending. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Interview Summary

Applicants would like to thank Examiners Epperson and Celsa for the courtesy of a personal interview of May 24, 2005, at which the rejections of record and the Rowlands, Zauderer, and Waterhouse references were discussed.

Restriction/Election

The Examiner has acknowledged Applicants response (with traverse) to the Restriction and/or Election of Species Requirements filed on November 8, 2004. (*See* Office Action at page 2, sections 3-5.) With respect to the Election of Species requirement, the Examiner has withdrawn claims 48 and 52 from further consideration "as being drawn to a non-elected species because Applicants' elected modified phenotype is not 'nonadherence' as indicated in claim 48, but rather 'cell death caused by expression of a suicide gene'." (Office Action at page 3.) The Examiner further stated that "Applicants' elected species for modified phenotype is not a 'combination' of 'nonadherence' and 'cell death' as disclosed in claim 52." *Id.* Applicants respectfully traverse, and disagree with the examiner's characterization of the election of species.

The modified phenotype of nonadherence in the present specification and claims is generic to cell death and cell death caused by expression of a suicide gene. Paragraph [0243] of the specification states that: "[f]or example, if host cells are chosen which grow attached to a solid support, those host cells which succumb to cell death and/or undergo a lytic event will be released from the support and can be recovered in a supernatant." (Specification at page 96, paragraph [0243].) Thus, cells that undergo cell death become nonadherent to the substrate. As such, Applicants respectfully request that the Examiner consider claims 48 and 52.

Information Disclosure Statement

The Examiner has requested additional copies of the Information Disclosure Statements filed on September 22, 2003, July 1, 2003, and August 13, 2002, because his copies are not readable. Applicants respectfully submit that legible copies of these

documents were filed on the respective dates, but further to the Examiner's request, provide herewith copies of these documents as originally filed, along with a copy of the postcard receipt bearing the date stamp of the USPTO acknowledging receipt of the documents.

Rejections under 35 U.S.C. § 112, 1st Paragraph—Written Description

Claims 1-20, 22, 24-27, 29-35, 38, 40-41, 44, and 59-62 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey that the inventors had possession of the claimed invention at the time the application was filed. (Office Action at page 7, section 17.) Applicants respectfully traverse this rejection.

The Examiner asserted that "[t]he scope of this claim includes an enormous number of methods using an enormous number of potential vectors wherein said vectirs [sic] are not limited in any way ... produced by an unspecified number of methods. Consequently, the nature of the invention cannot be fully determined." (Office Action at pages 7-8.) Applicants respectfully disagree with this assertion.

The Examiner, himself, pointed to paragraphs [0123] and [0124] in the specification as filed, which provides a listing of types of vectors suitable for use in the present invention. In particular, and as quoted by the Examiner, the specification states that "[i]n constructing antibody libraries in eukaryotic cells, any standard vector which allows expression in eukaryotic cells may be used." (Specification at page 54, paragraph [0123].) The specification goes on to provide, more specifically, a listing of the types of eukaryotic virus vectors that are suitable for use in the present invention. (Specification at pages 54-55, paragraph [0124].) Furthermore, the fact that they are designated as

standard vectors indicates that such vectors were known in the art. As such, they need not be described in the specification. *See Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986) (holding that the description need only describe what is new or non-conventional); M.P.E.P §2163, p. 2100-171, col. 1 (Rev. 2, May 2004). Hence, contrary to the Examiner's assertions, the specification does provide a clear indication to one of ordinary skill in the art what the nature of the invention is, and that Applicants were in possession of the claimed invention at the time the application was filed.

The Examiner also asserted that "[a]lthough the specification discloses examples of 'tri-molecular recombination' ... the specification and claims do not provide ***any*** examples for other processes like direct ligation and homologous recombination that would likewise yield a 'library' of antibodies upon expression," and that "Applicants have not provided a 'representative' number of examples to show that they were in possession of the full scope of the claims." *Id.* (emphasis in original). Furthermore, the Examiner asserted that "the prior art teaches that only poxvirus vectors that possess genomes capable of undergoing trimolecular recombination ... will reliably produce recombinants at an efficiency that is amenable for polynucleotide library construction." *Id.* at 10.

The Examiner further asserted that the specification teaches that "libraries of polynucleotides that encode potential antigen-specific human immunoglobulins generally cannot be produced using "traditional' methods of homologous recombination with poxviruses like vaccinia," and that 'direct ligation' was [also] shown to be unsatisfactory ... ." (Office Action at pages 9-10). The Examiner cited Seed, B., "Developments in Expression Cloning," *Current. Op. Biotech.* 6: 567-573 (1995)., to suggest that "a person of skill in the art would not expect all vectors to behave the same (e.g., plant

viruses require different considerations than animal viruses and double stranded DNA does not behave the same as single stranded RNA)." *Id.* at 10. Applicants respectfully disagree with the Examiner's assertions.

First, Applicants respectfully remind the Examiner that the written description requirement is met if one skilled in the art could reasonably conclude that the inventor had possession of the claimed invention in the specification as filed. *See Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563, 19 U.S.P.Q.2d 1111, 1116 (Fed. Cir. 1991); M.P.E.P. §2163.02. The Examiner cited *University of California v. Eli Lilly and Co.* 43 U.S.P.Q.2d 1398 (Fed. Cir. 1997) for the proposition that adequate disclosure requires a ***representative number of examples***. (*See* Office Action at page 8.) However, Applicants respectfully submit that this is an inappropriate characterization of *Eli Lilly*. There is no discussion in *Eli Lilly* that, in order to meet the requirements for adequate disclosure under the patent laws, an applicant must provide a representative number of ***examples***. Rather, the Federal Circuit in *Eli Lilly* set forth several possible tests for determining whether a claimed genus is adequately described, one of which was the "representative number of ***species***" test. *See Eli Lilly* at 1406. Moreover, the Federal Circuit and the PTO have acknowledged that a specification may adequately describe a genus even though it fails to describe a single species falling within the genus. *Eli Lilly* at 1406; M.P.E.P. 2163 (II)(A)(3)(a)(ii) at 2100-169.

Given the disclosure in the present specification, Applicants respectfully submit that the claims are not overly broad, and that one of ordinary skill could reasonably conclude that the inventors had possession of the claimed methods in the specification as filed. Nevertheless, in an effort to facilitate prosecution, and not in acquiescence to the Examiner's rejection, Applicants have amended claim 1 to recite that, wherein the first or

second library is constructed in a poxvirus vector, said first or second library is not constructed by traditional homologous recombination.

However, Applicants respectfully submit that the Examiner has mischaracterized the specification with respect to the use of other library construction methods, e.g., direct ligation. While the specification does indicate that direct ligation results in a relatively low recombination efficiency and titer (*see* Specification at paragraphs [0021] and [0163]), it does not say that methods such as direct ligation or modified homologous recombination cannot be used to generate vaccinia virus expression libraries, as suggested by the Examiner. Furthermore, while these methods may not be as efficient as tri-molecular recombination, there is no requirement in the claims for a particular titer or recombination efficiency. Thus, contrary to the Examiner's insertion of such a statement into a quotation from the specification, the specification does not say that "only vaccinia virus vectors that are amendable [sic] to 'tri-molecular' recombination will work." (*See* Office Action at page 11.)

With respect to the Examiner's assertion that "the specification and claims do not provide **any** examples for other processes like direct ligation and homologous recombination," (Office action at page 8) (emphasis in original), Applicants respectfully submit as set forth above, that there is no requirement for a representative number of examples to support an adequate written description. Furthermore, the use of direct ligation and homologous recombination to insert a heterologous genetic element into a vector were known in the art, as evidenced by paragraphs [0017]-[0021] of the specification. As such, they need not be described in the specification. *See Hybritech,* 802 F.2d at 1384, 231 USPQ at 94; M.P.E.P §2163, p. 2100-171, col. 1 (Rev. 2, May 2004). Also, even though not required, the specification does provide an example of

modified homologous recombination. Example 4 describes the use of *modified* homologous recombination to produce recombinant vaccinia viruses, and shows that the method has a 35-fold improvement in frequency of viral recombinants over traditional homologous recombination. (Specification at paragraphs [0324]-[0328]). Moreover, the present specification describes selection of specific human intrabodies from cDNA libraries constructed in different systems; namely adenovirus, herpesvirus, or retrovirus vectors. *See* Example 3 of Specification, paragraphs [0316]-[0321]. As such, the specification as filed provides a representative number of species of methods for constructing expression libraries.

With respect to the Seed article cited by the Examiner, Applicants respectfully submit that, while Seed identifies some differences between expression systems, he also identifies strategies for overcoming some of the problems associated with those expression systems (Seed at 570, column 1, 2nd full paragraph) ("One strategy to minimize these problems has been to avoid multiple rounds of retroviral transcription, reverse transcription, and integration. ... Use of a highly transfectable cell line with an [sic] simian virus 40 (SV40)-based replication boost ... has allowed primary titers in the order of 10^6 infectious particles per millimeter.") Thus, even assuming that one of skill in the art would expect some differences, as set forth above, the vectors suitable for use in the present specification are standard vectors that allow expression in eukaryotic cells (*see* Specification at pages 54-55, paragraphs [0123]-[0124]), and therefore, under *Hybritech*, need not be described in the specification.

Given the disclosure in the present case, one of ordinary skill in the art could reasonably conclude that the inventors had possession of the claimed methods when the

application was filed. Accordingly, the claimed invention is adequately described, and Applicants respectfully request reconsideration and withdrawal of this rejection.

Rejections under 35 U.S.C. § 112, 1st Paragraph--Enablement

Claims 1-20, 22, 24-27, 29-35, 38, 40-41, and 59-62 are rejected under 35 U.S.C. § 112, first paragraph, because, the specification allegedly does not enable a person skilled in the art to which it pertains to make and use the invention commensurate with the scope of the claims. (Office Action at page 12.) Applicants respectfully traverse this rejection.

The test of enablement is whether one of ordinary skill in the art, given the disclosure at the time of filing, could make and use the claimed invention without undue experimentation. *See In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). The Examiner addressed several of the "*Wands*" factors to be considered when determining whether experimentation is "undue." *See id.*; (Office Action at page 12). As stated in *Wands*, "'[t]he key word is "undue," not "experimentation."'" *Wands* at 737 (quoting *In re Angstadt*, 537 F.2d at 504, 190 USPQ at 219).

A) Breadth of the claims and nature of the invention

With respect to the breadth of the claims and the nature of the invention, the Examiner argued that:

> The claims are drawn to a broad genus. The scope of these claims include an enormous number of methods for producing and/or selecting intracellular immunoglobulins using an enormous number of potential vectors ... Consequently, the nature of the invention cannot be fully determined.

(Office Action at page 13). Applicants respectfully disagree with the Examiner's argument. The Examiner has basically repeated the assertions made with respect to written description. As discussed in detail in the preceding section of this Reply, Applicants have provided disclosure that teaches several methods to construct a library in various types of vectors, and teaches how to select a vector containing the insert of interest. Therefore, Applicants respectfully submit that the nature of the invention can be fully determined.

B) State of the prior art and level of predictability in the art

With respect to the state of the prior art and level of predictability in the art, the Examiner repeated the incorrect assertion that "only vaccinia virus vectors that are amendable [sic] to 'tri-molecular' recombination will work." (Office Action at page 14.) Applicants respectfully disagree with this assertion. As discussed *supra* with respect to written description, although methods such as direct ligation and modified homologous recombination may be less efficient than tri-molecular recombination for constructing a library in vaccinia virus, the specification does not say that they cannot be used. As stated above, direct ligation was known in the art, and Example 4 in the present specification describes the use of modified homologous recombination for making recombinant vaccinia virus.

The Examiner has also repeated the assertion that "a person of skill in the art would not expect all vectors to behave the same," citing the Seed article to support this proposition. (Office Action at page 14.) As Applicants respectfully submitted, *supra*, Seed also identifies that there methods known in the art to overcome problems associated with retroviral vectors. Furthermore, the present specification provides disclosure

regarding construction of cDNA libraries in adenovirus, herpesvirus and retrovirus vectors. See Specification, Example 3, paragraphs [0316]-[0321].

Therefore, contrary to the Examiner's assertions, the state of the art and level of predictability in the art do not support the conclusion that methods other than tri-molecular recombination could not be used to produce vaccinia virus vectors, or that the no other vectors could be expected to work.

C) Amount of direction provided by inventor and existence of working examples

With respect to the amount of direction provided by the inventor and the existence of working examples, the Examiner asserted that

> Applicants disclose the use of examples that contain "two" non-overlapping fragments of the v7.5/tk virus genome produced using the NotI and ApaI restriction enzymes and "one" recombinant plasmid containing TLK/TKR and the library of human immunoglobulin genes to produce the vaccinia virus vectors.

(Office Action at page 15.) Applicants respectfully remind the Examiner that "[t]he specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation." M.P.E.P. § 2164.02 at 2100-187 (citing *In re Borkowski*, 422 F.2d 904, 908, 164 U.S.P.Q. 642, 645 (CCPA 1970)). Furthermore, in the present case, as acknowledged by the Examiner, Applicants do provide examples, even though they are not required. However, the disclosure is not limited to the examples. "How a teaching is set forth, by specific example or broad terminology, is not important." M.P.E.P. § 2164.08 at 2100-198 (citing *In re Marzocchi*, 439 F.2d 220, 223-24, 169 USPQ 367, 370 (CCPA 1971)). As set forth, *supra*, the present specification provides extensive disclosure on how to make and use vectors, including vaccinia virus vectors (*see, e.g.*,

Specification at pages 54-69, paragraphs [0123]-[0162]; pages 69-83, paragraphs [0163]-[0198] (tri-molecular recombination); Example 3, pages 128-130, paragraphs [0316]-[0321]; Example 4, pages 130-140, paragraphs [0322]-[0342]). Thus, there is ample direction provided in the present specification, some in the form of examples.

D) Quantity of experimentation needed to make or use invention

With respect to the quantity of experimentation needed to make or use the invention based on the content of the disclosure, the Examiner asserted that:

> As a result of the broad and unpredictable nature of the invention and the lack of specific guidance from the specification, the Examiner contends that the quantity of experimentation needed to make and[/]or use the invention would be great.

(Office Action at page 15.) Applicants respectfully disagree with the Examiner's assertions.

First, the fact that some experimentation may be required does not preclude enablement, so long as the experimentation is not undue. *Wands*, 858 F.2d at 736-737. "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *Id.* at 737. Second, contrary to the Examiner's assertions, as stated above, the specification does provide specific guidance to practice the invention, including, but not limited to, guidance regarding immunoglobulins, in particular, intracellular immunoglobulins (*see, e.g.,* Specification at paragraphs [0047]-[0083]), antigens (*see, e.g.,* Specification at paragraphs [0104]-[0112]), heterologous sequences, *e.g.*, targeting sequences, (*see, e.g.,* Specification at paragraphs [0084]-[0103]), transcriptional control

regions (*see, e.g.,* Specification at paragraphs [0065]-[0066]), vectors (*see, e.g.,* Specification at paragraphs [0123]-[0162]),and selection and screening strategies for isolating recombinant intracellular immunoglobulin molecules (*see, e.g.,* Specification at paragraphs [0199]-[0229]), as well as methods of constructing libraries using modified homologous recombination, direct ligation, and tri-molecular recombination (*see, e.g.,* Specification at paragraphs [0163]-[0198]). In addition, the specification provides illustrative, non-limiting examples of specific embodiments of the present invention (*see, e.g.,* Specification at paragraphs [0300]-[0413]).

The Examiner further asserted that "Applicants have not provided any working examples that would teach this enormous genus that falls within a highly unpredictable art area." (Office Action at page 16.) Applicants respectfully disagree with the Examiner's assertions. Working examples are not required in order to comply with the enablement requirement of 35 U.S.C. § 112, 1st paragraph. *See, e.g.*, M.P.E.P. § 2164.02. As the Examiner, himself, stated, "there must be sufficient disclosure, *either through illustrative examples or terminology*, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed." (Office Action at page 15) (citing *In re Vaeck*, 947 F.2d 488, 496 & n.23, 20 U.S.P.Q.2d 1438, 1445 & n.23 (Fed. Cir. 1991)) (emphasis added).) In the present case, as detailed above with specific references to the specification as filed, Applicants have provided examples and terminology sufficient to teach one of ordinary skill in the art to practice the methods of the present invention.

The analysis of the various factors for determining whether the experimentation required to practice the claimed invention would be undue, clearly shows that it would not be. Namely, the claims are not overly broad in light of the extensive disclosure of

the various aspects of the invention. Moreover, the state of the art and level of predictability in the art at the time of filing were such that, given the disclosure, one of ordinary skill in the art could practice the invention. Furthermore, one of ordinary skill in the art, given the specification, could make and use the invention without undue experimentation because there is ample direction provided in the specification, and there are examples to illustrate various aspects of the present invention. The weighing of these factors indicates that the claims are enabled. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

Rejections under 35 U.S.C. § 112, 2nd Paragraph

Claims 27, 29-35, 38, 40, 41, and 44 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particular point out and distinctly claim the subject matter which Applicants regard as their invention. (Office Action at page 16.) Applicants respectfully traverse this rejection.

With respect to claim 27 and the claims that depend therefrom, the Examiner asserted that there is insufficient antecedent basis for the term "the naturally-occurring genome" in the first line. *Id.* Applicants respectfully disagree with this assertion and respectfully submit that, since "the naturally-occurring genome" as recited in the claim refers to a property or feature of the vector. As such, the use of the article "the" is appropriate.

With respect to claim 35 and the claims that depend therefrom, the Examiner asserted that there is insufficient antecedent basis for the term "said host cells," because "more than one host cell is referred to in the independent claim." *Id.* Applicants believe that the claim as originally filed, when read in light of the specification, would

reasonably apprise one skilled in the art of the metes and bounds of the claimed invention. Nevertheless, without narrowing the scope of the claim, Applicants have amended claim 35 to recite: " said population of eukaryotic host cells is permissive," thereby making explicit that which was at least implicit.

The Examiner's grounds of rejection of claims 27, 29-35, 38, 40, 41, and 44 under 35 U.S.C. § 112, second paragraph, have been addressed by Applicants, and it is believed that this rejection has been fully accommodated. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection.

Rejections under 35 U.S.C. § 103

Claims 1-20, 22, 24-27, 29-35, 38, 40-41, 44 and 59-61 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Rowlands *et al.*, WO 93/01296 (hereinafter "Rowlands"), Zauderer, WO 00/28016 (hereinafter "Zauderer"), and Waterhouse *et al.*, *Nuc. Acids Res. 21*: 2265-66 (1993) (hereinafter "Waterhouse"), as evidenced by Roitt *et al.*, IMMUNOLOGY 67 (6th ed., 2001) (hereinafter "Roitt") and Applicants' specification. (Office Action at Pages 17-18, Section 22.) Applicants respectfully traverse this rejection.

In particular, the Examiner asserted that:

> It would have been obvious to one skilled in the art at the time the invention was made to make a library of vaccinia virus vectors as taught by Zauderer et al. to express fully functional antibodies as taught by Rowlands et al. for the purpose of screening and/or affinity maturation as taught by Waterhouse et al. because Zauderer et al. explicitly state that their libraries can be efficiently produced using the tri-molecular recombination approach with the vaccinia virus vectors (like the vaccinia virus vectors disclosed by Rowlands et al.) and Waterhouse et al. teach that such a library would be useful in screening and affinity maturation. Applicants respectfully disagree with these assertions.

(Office Action at pages 23-24.)

Section 2143 of the M.P.E.P. sets forth the basic requirements for a *prima facie* showing of obviousness:

> First, there must be some suggestion or motivation, whether in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference. . . must teach or suggest all the claim limitations.

The M.P.E.P further states that "[t]he teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure." *Id.* Applicants respectfully assert that the Examiner has not met these requirements to establish a *prima facie* case of obviousness.

First, the combination of Rowlands, Zauderer, and Waterhouse does not teach or suggest all of the limitations of the claims. In particular, the cited references do not teach or suggest the introduction of <u>two</u> expression libraries into <u>eukaryotic</u> host cells. Rowlands discloses the introduction of vaccinia virus expression vectors containing the heavy and light chain sequences of a single, previously known and identified antibody, Campath-1H. Zauderer discloses the introduction of one library expressing tumor, cancer, or infected cell-specific antigens. Waterhouse discloses the introduction into bacterial host cells of bacteriophage vectors encoding immunoglobulin heavy and light chain variable region fragments that can undergo Cre-*lox* regulated site-specific recombination, and suggests that the system can be used to generate large combinatorial libraries by providing repertoires of heavy and light chain fragments. Furthermore, these references do not teach selection of intracellular immunoglobulins. While Rowlands indicates that some of their heavy and light chains failed to be secreted into the culture

medium, this is not the same as forming and selecting an intracellular immunoglobulin, particularly since they were attempting to achieve secretion of Campath-1H antibodies.

Second, there was no suggestion or motivation to combine Rowlands, Zauderer, and Waterhouse to arrive at the claimed invention. The Examiner contended that:

> . . . one of ordinary skill in the art would have been motivated to make the libraries as taught by Zauderer et al. using the heavy/light chain antibodies as disclosed by Rowlands et al. because Zauderer et al. explicitly state that the [sic] their "tri-molecular" approach represents and easy and efficient means for generating a library in vaccinia virus vectors in mammalian cells, which is a preferred embodiment for Rowlands et al. . . . In addition, Waterhouse et al. teach that "associated" light and heavy chains are a "preferred" embodiment for screening and/or affinity maturation because they can be "simultaneously co-selected" . . ., which would encompass the "associated" heavy/light chains described by Rowlands et al.

(Office Action at page 24) (citations omitted). Applicants respectfully disagree with this contention and remind the Examiner that "[t]he mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the *desirability* of the combination." M.P.E.P. § 2143.01, p. 2100-131, 1st column (Rev. 2, May 2004) (citing *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990) (underline in original) (italics added).

There is nothing in Rowlands, Zauderer, or Waterhouse that would have motivated or suggested to one of ordinary skill in the art the desirability of combining these references. While Rowlands describes the expression of a single, previously known and identified recombinant antibody using a vaccinia virus vector, there is no suggestion provided therein that would have motivated one of ordinary skill in the art to introduce two expression libraries encoding intracellular immunoglobulin subunit polypeptides into eukaryotic cells. Furthermore, while Zauderer describes the

introduction of a single expression library of tumor, cancer, or infected cell-specific antigens, there is no suggestion to one of ordinary skill in the art that this could be used in conjunction with the Rowlands method of making a single known antibody to introduce two expression libraries encoding intracellular immunoglobulins and select a previously unknown antibody as in the present invention. This is particularly the case in light of the fact that Rowlands does not describe an intracellular antibody. Finally, Waterhouse does not even describe eukaryotic host cells; rather, Waterhouse suggests the generation of large bacteriophage antibody repertoires and subsequent infection into *bacterial hosts* for phage display. Phage display requires that the immunoglobulins be presented as fragments on the surface of a bacteriophage. The selection of a bacteriophage which carries an antigen-specific fragment is not performed intracellularly in eukaryotic cells. Thus, although Waterhouse may suggest the introduction of separate repertoires of heavy and light chain variable region fragments, there is nothing in Waterhouse to suggest to one of ordinary skill in the art to introduce two expression libraries into eukaryotic cells for selecting polynucleotides which encode an intracellular immunoglobulin molecule or a fragment thereof, as in the present invention. There is no basis for concluding that an invention would have been obvious solely because it is a combination of elements that were known in the art at the time of the invention. *See Fromson v. Advance Offset Plate, Inc.*, 755 F.2d 1549, 1556 (Fed. Cir. 1995). Since there is no suggestion or motivation to combine Rowlands, Zauderer, and Waterhouse, they cannot properly be combined to render the claimed invention obvious.

As further evidence that one of ordinary skill in the art would not have been motivated to combine Rowlands, Zauderer, and Waterhouse, submitted herewith as EXHIBIT B is a copy of the Declaration of Dr. Maurice Zauderer from co-pending U.S.

Application Serial No. 09/987,456 ("the '456 application"), and the documents that were submitted as EXHIBITS B1-B4, therewith. As evidenced by his *curriculum vitae* attached to his Declaration, Dr. Zauderer, a co-inventor on the present application as well as the '456 application, is currently the President and CEO of Vaccinex, Inc., and is an expert in the fields of immunology and cell biology. Dr. Zauderer provided his opinion that there was no motivation or suggestion for one of ordinary skill in the art to combine Rowlands, Zauderer, or Waterhouse to arrive at the claimed invention in the '456 application because: 1) Rowlands does not teach or suggest introduction of libraries into eukaryotic cells; 2) Zauderer does not teach or suggest introduction into eukaryotic host cells of two expression libraries that separately encode immunoglobulin heavy and light chains; and 3) Waterhouse describes phage display techniques, which one of ordinary skill in the art would not have considered as features that could be extrapolated to eukaryotic systems. *See* EXHIBIT B at Paragraph 15. Given Dr. Zauderer's opinion that one of ordinary skill in the art would not have found a suggestion or motivation to combine Rowlands, Zauderer, and Waterhouse to arrive at the immunoglobulin selection technology presented in the '456 application, *a fortiori*, there would have been no suggestion or motivation for one of ordinary skill in the art to combine these references to arrive at a selection system for *intracellular* immunoglobulins that uses two separate expression libraries and that induces a modified phenotype in the host cell as in the presently claimed invention.

Even assuming, *arguendo*, that one of ordinary skill in the art would have been motivated to combine Rowlands, Zauderer, and Waterhouse, there would not have been a reasonable expectation of success in doing so to arrive at the present invention. The Examiner contends that "Zauderer et al. teach several successful examples of library

formation using the same vaccinia virus vectors that are disclosed by Rowlands et al. and Waterhouse et al. teach several successful examples of associated light/heavy chains that can be used for screening and/or antibody maturation, which would encompass the heavy/light chain antibodies disclosed by Rowlands et al." (Office Action at page 24.) Applicants respectfully disagree with the Examiner's contentions.

One of ordinary skill in the art would not have reasonably expected that the phage display technology described in Waterhouse could be extrapolated to methods of introducing two random expression libraries into eukaryotic host cells for selecting a previously unknown intracellular immunoglobulin as in the present invention. As stated above, Waterhouse describes the generation of a phage library, which involves the use of filamentous bacteriophage as a vector, and bacterial cells as hosts, and the immunoglobulin fragments expressed in phage display must form part of a fusion protein with a phage protein. In contrast, the vaccinia virus vectors used in Rowlands and Zauderer are from an animal virus and are introduced into eukaryotic host cells for expression. Given these different vectors and the difference in prokaryotic versus eukaryotic host cells, one of ordinary skill in the art would not have expected any selection methods described in Waterhouse to be useable with vectors that express in eukaryotic hosts because there would be different conditions required for the two systems.

In fact, the present specification distinguished phage display methods because it suffers from many drawbacks as compared to the present invention (*See* Specification, paragraph [0006]) ("Phage display methods normally result in the expression of an antigen-binding fragment of an immunoglobulin molecule, thus, after phage selection, the immunoglobulin coding regions from the phage must be isolated and re-cloned to

generate whole antibodies, or antigen binding fragments, and expressed in any desired host cell to test for the ability to function as an intrabody.")) Thus, an immunoglobulin would have to be identified and selected in a prokaryotic system by phage display, then cloned into a eukaryotic expression vector, and tested to determine if its expression induces a modified phenotype in a eukaryotic host cell.

Furthermore, one of ordinary skill in the art would not have expected from Zauderer, which discloses introduction of one library into eukaryotic host cells, and Rowlands, which discloses the expression of a previously identified antibody from eukaryotic cells, that two separate libraries could be randomly introduced into eukaryotic host cells to efficiently form a plurality of immunoglobulin molecules from which an immunoglobulin molecule of interest could be identified and selected. Therefore, absent a reasonable expectation of success, the cited references cannot properly be combined to render the claimed invention obvious.

As further evidence that one of ordinary skill in the art would not have had a reasonable expectation of success in combining the cited references to arrive at the claimed invention, submitted herewith as EXHIBIT A is a copy of the Declaration of Dr. Walter J. Storkus from co-pending U.S. Application Serial No. 09/987,456 ("the '456 application"), and the documents that were submitted as EXHIBITS A1-A3, therewith. As evidenced by his *curriculum vitae* attached to his Declaration, Dr. Storkus is currently a tenured professor in the Departments of Immunology and Dermatology at the University of Pittsburgh, and is an expert in the field of immunology. Dr. Storkus provided his opinion that, when the idea of an antibody selection system using two separate random libraries of eukaryotic expression vectors to identify immunoglobulins of interest as disclosed in the '456 application was first proposed to him as a member of the Scientific

Advisory Board (SAB) of Vaccinex, Inc., he was skeptical that the technology would work to select antigen-specific immunoglobulins. *See* EXHIBIT A at Paragraph 6. In particular, Dr. Storkus stated that he did not expect that good antibodies could be selected in eukaryotic cells because, *inter alia*, he thought that there would be limitations on the throughput for screening libraries expressed in eukaryotic cells, and because it was thought that random pairs of immunoglobulin heavy and light chains, when expressed, would not associate properly in the eukaryotic cytoplasm. *Id.* at Paragraph 7. He also indicated that his expectations for success would not have changed in view of Rowlands, Zauderer and Waterhouse. *Id.* at Paragraph 9. Given his initial skepticism for the immunoglobulin selection technique using two expression libraries in eukaryotic cells, *a fortiori*, one of ordinary skill in the art would not have expected that a selection system for *intracellular* immunoglobulins that uses two separate expression libraries and that induces a modified phenotype in the host cell would work.

Since there was no suggestion or motivation to combine Rowlands, Zauderer, or Waterhouse, and no reasonable expectation of success from the combination, a *prima facie* case of obviousness is not established. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection.

Claims 1-20, 22, 24-27, 29-35, 38, 40-41, 44 and 59-61 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Rowlands, Zauderer, Waterhouse, and Marasco, W.A. "Intrabodies: Turning the humoral immune system outside in for intracellular immunization," *Gene Therapy 4*: 11-15 (1994) (hereinafter "Marasco"), as evidenced by Roitt and Applicants' specification. (Office Action at page 25, Section 23.) Applicants respectfully traverse this rejection.

Specifically, the Examiner contended that "[f]or claims 1-20, 22, 24-27, 29-35, 38, 40-41, 44, and 59-61, Rowlands et al. and Zauderer et al. teach all the limitations stated in the 35 U.S.C. 103(a) rejection above ..., which renders obvious claims 1-20, 22, 24-27, 29-35, 38, 40-41, 44 and 59-61." (Office Action at page 25) (bold emphasis omitted). The Examiner stated that "for claim 62, the combined prior art teachings of Rowlands et al. and Zauderer et al. differ from the claimed invention by not reciting the use of targeting sequences capable of localizing said intracellular immunoglobulin molecule." *Id.* (bold emphasis omitted). However, the Examiner asserted that "Marasco ... teaches, for example, localization in the endoplasmic reticulum using a KDEL-tagged sFv intrabody," and that:

> [i]t would have been obvious to one skilled in the art at the time the invention was filed to screen the libraries of antibodies disclosed by the combined teachings of Rowlands et al. and Zauderer et al. using intracellularly expressed and/or localized antibodies like the KDEL-tagged sFV disclosed by Marasco because Marasco explicitly states that such "intrabodies" represent a "...powerful new family of protein molecules that have potential application in the gene therapy of a number of human diseases."

Office Action at page 26. Applicants respectfully disagree with these contentions.

First, as set forth above with respect to the 103(a) rejection over Rowlands, Zauderer, and Waterhouse, there was no motivation to combine Rowlands and Zauderer, and no reasonable expectation of success from the combination. Therefore, claims 1-20, 22, 24-27, 29-35, 38, 40-41, 44 and 59-61 are not obvious under 35 U.S.C. § 103(a) over Rowlands and Zauderer.

Second, with respect to claim 62, the addition of Marasco to the combination of references does not render obvious claim 62 (or any of the other claims, for that matter). First, there is no teaching or suggestion in Marasco or Rowlands or Zauderer to combine

these references. Marasco discloses the use of intrabodies for therapeutic applications such as gene therapy for human diseases. While the Examiner lists several potential uses of intrabodies as set forth in Marasco, none of them are for methods of selecting polynuclotides encoding intracellular immunoglobulins from first and second expression libraries as in the present invention. Thus, there is no suggestion that Marasco could be combined with the expression libraries of Zauderer (which does not disclose expression libraries encoding intracellular immunoglobulins), or the single, recombinant antibody in vaccinia virus as in Rowlands to arrive at the present invention.

The Examiner, quoting Marasco (in part) further asserts that one of ordinary skill in the art would have a reasonable expectation of success because:

> Marasco teaches that "the creation of large human immunoglobulin libraries **[like in the in vitro libraries disclosed by the combined teachings of Rowlands et al. and Zauderer et al.]** ... has allowed investigators to bypass in vivo immunization and produce high-affinity human antibodies to human proteins."

Office Action at page 26. (bold emphasis to Examiner's insertion into the quotation added). However, Applicants respectfully disagree and submit that this is a mischaracterization of Marasco. Namely, the portion of the quote from Marasco that was replaced with the Examiner's own text provides the phrase: "and when combined with ***phage display technology***, has allowed investigators to bypass in vivo immunization and produce high-affinity human antibodies to human proteins" (Marasco, Introduction at page 11, column 1, first paragraph.) As set forth above with respect to Waterhouse, the phage display technique referenced by Marasco involves filamentous bacteriophage vectors and bacterial hosts and, therefore, is <u>not</u> like *in vitro* libraries that the Examiner alleges are taught by the combined teachings of Rowlands

and Zauderer (which, as Applicants have shown above, would not have been combined by one of ordinary skill in the art), and certainly is not like the expression libraries of the present invention. Rather, under Marasco, the intrabody would have to be identified and selected from phage display, cloned into a eukaryotic expression vector, and tested for use as an intrabody. Furthermore, this passage from Marasco is a general disclosure about manipulation of human antibody genes, not a description of how to select an from expression libraries intracellular immunoglobulin whose expression induces a modified phenotype in a eukaryotic host cell.

Since there was no suggestion or motivation to combine Rowlands, Zauderer, or Marasco, and no reasonable expectation of success from the combination, a *prima facie* case of obviousness has not been established. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection.

Rejection Based on Non-Statutory Obviousness-Type Double Patenting

In the Office Action at pages 27-29, the Examiner has provisionally rejected claims 1-20, 22, 24-27, 29-35, 38, 40-41, 44, and 59-62, for alleged obviousness-type double patenting over claims 84-122 and 127-131 of commonly-owned U.S. Patent Application Serial No. 09/984,456 ("the '456 application") and Marasco. Applicants respectfully request that this rejection be held in abeyance until such time as otherwise patentable subject matter has been identified in either the present application or the '456 application. At that time, Applicants will consider filing a terminal disclaimer to obviate the double-patenting rejection.

In the Office Action at page 30, the Examiner has also provisionally rejected claims 1-20, 22, 24-27, 29-35, 38, 40-41, 44, and 59-62, for alleged obviousness-type double patenting over claims 46-133 of commonly-owned U.S. Patent Application Serial No. 10/465,808 ("the '808 application") and Marasco. Applicants respectfully request that this rejection be held in abeyance until such time as otherwise patentable subject matter has been identified in either the present application or the '808 application. At that time, Applicants will consider filing a terminal disclaimer to obviate the double-patenting rejection.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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